Docket No.: ALXN-P02-089
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Figdor et al.

Application No.: 10/625,202 | Confirmation No.: 1242

Filed: July 23, 2003 | Art Unit: 1648

For: COMPOSITION AND METHOD FOR MODULATING DENDRITIC CELL-T CELL INTERACTION | Examiner: M. G. Hill

REPLY BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. § 41.41(a), appellants are filing this Reply Brief in response to the Examiner's Answer dated August 5, 2010 (hereinafter "the Examiner's Answer"), and in support of their appeal from the rejection of claims 1, 3, 4, 6, 7, 19 and 23-27 in the Final Office Action dated October 6, 2009 and the Advisory Action dated January 5, 2010. Appellants previously filed a Pre-Appeal Brief and Notice of Appeal on February 4, 2010, and an Appeal Brief on May 5, 2010, in connection with this case.

I. Introduction

Appellants maintain that claims 1, 3, 4, 6, 7, 19 and 23-27 of the present application are patentable.

In particular, appellants maintain the position that claims 1, 3, 4, 6, 7, 19 and 23-27 of the present application are enabled.

Appellants submit that the Examiner's Answer is insufficient as a matter of law to uphold the rejections for at least the reasons set forth in appellants' Appeal Brief. Appellants have filed this Reply Brief to address the arguments raised by the Examiner in the Examiner's Answer, and to further demonstrate the patentability of appellants' claims 1, 3, 4, 6, 7, 19 and 23-27.

II. Summary of the Examiner's Answer

The Examiner's Answer maintains the §112 rejection of claims 1, 3, 4, 6, 7, 19 and 23-27 from the October 6, 2009 Final Office Action and the Advisory Action dated January 5, 2010 and restates the same grounds of rejection from that Office Action. The Examiner also cites a post-filing reference, *Geijtenbeek* et al., as showing that not all antibodies that bind the sequence have the same function, and further alleges that the enabling disclosure is not commensurate with the pending claims.

The Examiner's Answer provides a "Response to Arguments" section that addresses appellants' arguments presented in appellants' Appeal Brief. In particular, the Examiner first rejects appellants' arguments that no *prima facie c*ase of lack of enablement has been made because appellants' "assertions do not support the invention claimed." Next, the Examiner maintains that the method steps in the method of decreasing an immune response are not differentiated. Lastly, the Examiner asserts that appellant's arguments as to the disclosure are not commensurate with the invention claimed and that the "specification provides no teaching of the amount or type of reduced immune response or what the significance is *in vivo* or what the level of reducing produces."

III. Summary of the Appellants' Reply

Appellants' Appeal Brief fully addresses the grounds of rejection stated in the October 6, 2009 Final Office Action and the Advisory Action dated January 5, 2010. In particular, appellants contend that the Examiner has not met his burden of establishing a *prima facie* case of lack of enablement, and appellants' reasoning is well grounded in the case law as well as the MPEP, and supported by additional evidence. Appellants also maintain that the claimed invention directed to decreasing an immune response is differentiated by distinct method steps. Further, the specification teaches the *in vivo* significance of the claimed method.

This Reply Brief addresses the additional comments set forth in the Examiner's Answer. First, the Examiner's characterization of the post filing art, *Geijtenbeek* et al., appears erroneous. The Examiner's position that the enablement provided in the disclosure is not commensurate with the scope of the claims is also traversed. Next, the Examiner's response to appellant's arguments presented in the Appeal Brief is also addressed: 1) the Examiner misses the connection between the claimed invention and the additional evidence (i.e., *Ingulli* et al.; *Steinman*; *Pereira* et al.) appellants submitted with the Appeal Brief and how the additional evidence demonstrates the correlation between *in vitro* and *in vivo* results; 2) the Examiner misses the differentiating features between the claimed invention and alternative embodiments disclosed in the application; and 3) the Examiner's position that the pending claims do not define "the population by providing a specific included group but only include 'not infected with HIV' as the intended population"[1] overlooks the fact that it is clearly within the knowledge of one of ordinary skill in the art to determine the population in need of a reduced immune response. In sum, the disclosure is commensurate with the claimed inventions because it provides specific and sufficient guidance for one of ordinary skill in the art to practice the claimed invention.

Accordingly, appellants submit that the Board should find the final rejections of claims 1, 3, 4, 6, 7, 19 and 23-27 under 35 U.S.C. § 112 to be in error and should reverse the Examiner.

IV. Appellants' Reply to the Examiner's Answer

The specification teaches that dendritic cells (DC) "are professional antigen-presenting cells that capture antigens in the peripheral tissues and migrate via lymph or blood to the T cell area of draining lymph nodes and spleen. Here they present processed antigens to naïve T cells, initiating antigen-specific primary T cell responses." Paragraph [0022] of the instant application as published in No. 2005/0118168. Prior to the present invention, it was unclear how the DC-T cell contact is initiated and regulated." Paragraph [0024].

The application teaches that DC-SIGN, a C-type lectin receptor is the receptor of ICAM-3, an adhesion molecule expressed on the surface of resting T cells. The inventors were

[1] This appears to a new ground of rejection that is not present in the Final Office Action dated October 6, 2009 and Advisory Action dated January 5, 2010; it was, however, raised in the Office Action dated March 6, 2009. Appellants believe that this rejection should have been properly under the subheading of "New Grounds of Rejection" in the Examiner's Answer.

the first to establish the mechanism of interaction between dendritic cells and T cells.[2] The application further teaches that antibodies against DC-SIGN can inhibit the interaction between DC and ICAM-3, thereby inhibiting the clustering of DC and T cells, and the proliferation of resting T cells. *See* Examples 6 and 7. The application describes various assays in detail that one can employ to evaluate whether an anti-DC-SIGN antibody can inhibit the DC-ICAM-3 interaction, reduce DC-T cells clustering, and/or inhibit proliferation of resting T cells.

The Examiner's characterization of the post filing art, Geijtenbeek et al., appears erroneous.

The Examiner's starting position appears to be that "not all antibodies that bind the sequence have the same function" and the Examiner cites to Figure 2 of *Geijtenbeek* et al. to support that. However, a closer examination of that figure reveals two facts: 1) antibodies directed to different antigens showed different results; and 2) antibodies directed to the same antigen (i.e., DC-SIGN) showed the same results.

In particular, Figure 2 of *Geijtenbeek* showed experimental results with at least four different antibodies: two against DC-SIGN (AZN-D1 and AZN-D2), one against ICAM-3, and one against β2-integrin. As shown in Figure 2A, both anti-DC-SIGN antibodies inhibited DC adhesion to ICAM to about the same extent, whereas the anti-β2-integrin antibody did not. Further, Figure 2D showed when DC-SIGN was transiently expressed on COS7 cells, its adhesion to ICAM-3 was also blocked by the anti-DC-SIGN antibody AZN-D1, but not by the anti-β2-integrin antibody. Also shown in Figure 2D, the anti-ICAM-3 antibody blocked adhesion of the DC-SIGN-expressing COS7 cells with ICAM-3, but to a much lesser extent than the anti-DC-SIGN antibody.

Accordingly, the Examiner's interpretation of the post-filing art is erroneous. Figure 2 shows, contrary to the Examiner's assertion, that the anti-DC-SIGN antibodies do have the same function, and the antibodies that do not have that same function do not bind DC-SIGN.

[2] The finding that adhesion of DC to T cells is mediated by DC-SIGN was so significant that the related data was published in the highly renowned journal of *Cell*. *Geijtenbeek* et al., Cell 100, 575-585 (March 3, 2000). In addition, *Cell*, in the same issue, dedicated a minireview on DC-SIGN based on the concurrently published data in *Geijtenbeek* et al. and another article by *Geijtenbeek* et al. Steinman, Cell 100, 491-494 (March 3, 2000), submitted as Appendix E to the Appeal Brief, highlighted the new findings by *Geijtenbeek* et al.: "Despite their importance, the DC can be regarded as the Cinderella of the immune system, for years kept by the hearths of a few laboratories. With added attention, as illustrated by two papers by Geijtenbeek and colleagues in the issue of *Cell*, one can begin to appreciate some of the DC's glamor." *Id.* at 491.

The Disclosure Is Commensurate in Scope with the Pending Claims.

The Examiner's Answer also alleges that the "enabling disclosure is clearly not commensurate in scope with these claims." To support that, the Examiner states that the "specification only teaches AZN-D1 and D2 and *in vitro* assays" and that "the physiological art in general is acknowledged as unpredictable." Appellants respectfully disagree.

The pending claims recite "antibody which binds to a protein with the amino acid sequence of SEQ ID NO: 2 (DC-SIGN) on the surface of a dendritic cell, wherein said antibody reduces one or more interactions between a dendritic cell and a T cell thereby reducing said immune response in the animal . . . ." Thus, to practice the claimed invention, one would first identify antibodies that bind DC-SIGN and then select those antibodies that reduce the immune response.

As of the effective filing date of this application, i.e., January 20, 2000, it is indisputable that making antibodies against a known target requires merely routine experimentation. Further, the specification provides at least two antibodies that bind to DC-SIGN and teaches various assays in detail on how to determine whether such antibodies indeed inhibit interactions between a dendritic cell and a T cell. Accordingly, contrary to the Examiner's assertion, the specification provides ample guidance and specific teachings on how to generate antibodies that have the claimed function. The Examiner appears to require that the specification identify "specific regions the antibody binds to, or what the variants of the sequence are that can function and give rise to antibodies that have the same function." Appellants respectfully traverse and maintain that one of ordinary skill in the art, based on the state of antibody art in January 2000 and the detailed teachings in the instant application, does not need that level of specificity to arrive at an antibody having the claimed features.

The Examiner further cites MPEP 2164.03 with regards to the notion of predictability in the art. That same MPEP section provides:

> The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art.

MPEP 2164.03. Here, the application discloses that anti-DC-SIGN antibodies can inhibit adhesion between DC and T cells. It was known in the art that DC present processed antigens to T cells to initiate the T cell-mediated immune response. Thus, one skilled in the art can readily extrapolate the disclosed antibodies and assays (and their results) together with the knowledge of DC's involvement in immune responses to the claimed inventions. Further, the additional evidence appellants submitted with the Appeal Brief shows the *in vivo* predictability based on *in vitro* assays.

Predictability of the *in vitro* assays

The Examiner misses the connection between the claimed inventions and the additional evidence provided. Appellants submit that the additional evidence (i.e., *Ingulli* et al.; *Steinman*; *Pereira* et al.) provide the correlation between *in vitro* studies and *in vivo* results. However, the Examiner's Answer states that these references "show results or correlation with activating T-cells or increasing immune response, not the method claimed." Appellants respectfully disagree and address the Examiner's arguments with respect to each of these references.

The Examiner states that "Ingulli *et al.* show lymph nodes are removed to study cell interaction" and "[t]here is no showing of any immune response." First, the *Ingulli* et al. reference presents results from *in vivo* animal studies, which involves the use of confocal microscopy to track the *in vivo* location of fluorescent dye-labeled DC and T cells and observe the initial physical interaction between antigen-bearing DC and antigen-specific T cells. The lymph nodes are "harvested from sacrificed mice at various times after the DC injections" and then frozen and further processed for confocal microscopy. Thus, the lymph nodes are removed at the end of the *in vivo* studies to observe physical interaction between DC and T cells that took place *in vivo*. The authors concluded that the observed T cell/DC clusters represent antigen-presentation events, which coincided with T cell activation (e.g., as evidenced by IL-2 production), followed by proliferation and differentiation of the T cells, i.e., a T cell-mediated immune response. Accordingly, contrary to the Examiner's assertions, *Ingulli* et al. show the correlation between DC/T cell interactions and T cell-mediated immune response *in vivo*.

Further, the Examiner states that "the teachings of Steinman teach that DC and T-cell interaction induce an immune response, not the reduced immune response as now claimed."

First, the claims recite administering an antibody that binds DC-SIGN to inhibit the interaction between DC and T cell, thereby reducing the T cell-mediated immune response. The teachings in *Steinman* are consistent with the teachings of the specification that DC and T cells interact to produce an immune response, but that the antibodies set forth in the claims inhibit such an interaction and thereby reduce the immune response. Second, appellants contend that *Steinman* shows the correlation between *in vitro* and *in vivo* results: this reference provides a review of studies in the area of DC and immunity, discussing *in vivo* findings that corroborated *in vitro* results. *Steinman*, at 492, right column, 1st full paragraph.

With respect to another post filing reference, *Pereira* et al., *J. Immunother.* 30(7): 705-713 (October 2007), the Examiner states that the teachings "show they use antigen bound to antibody which is not required in the present claims and teach that AZN-D1 antibodies effectively induces an immune response . . . which is opposite the claimed invention . . . ." Appellants again respectfully traverse. *Pereira* et al. do not contradict the claimed invention at all. The reference shows that AZN-D1, one of the antibodies disclosed in the instant application, upon intravenous administration, indeed specifically targets DC-SIGN-positive cells in lymphoid tissues *in vivo*.

The Examiner appears to cite the following statement in *Pereira* et al. to support his position: "Recent in vitro studies have already shown that targeting antigens to APCs via a humanized anti-DC-SIGN antibody effectively induces antigen-specific immune response . . . ." However, a closer review of that statement indicates a reference to *Tacken* et al., "Effective induction of native and recall T-cell responses by targeting antigen to human dendritic cells via a humanized anti-DC-SIGN antibody" *Blood* (2005)106:1278-1285. *Tacken* et al. show that the humanized anti-DC-SIGN antibody conjugated with KLH, a model antigen, was capable of inducing T-cell responses at a 100-fold lower concentration than KLH alone. Thus, *Tacken* et al. do not contradict the claimed invention at all. In fact, this reference also confirms that the anti-DC-SIGN antibody can target DC-SIGN molecules on DC *in vivo*.

Appellants reiterate that the Examiner has failed to meet his burden of showing that the assertions made in the specification would note be believable to one of ordinary skill in the art. Regardless, Appellants cited these references to demonstrate that the *in vitro* results do correlate to *in vivo* effectiveness. The specification teaches various methods and assays to make and select antibodies that inhibit interactions between DC and T cells. It is textbook knowledge

in the art that DC and T cell interactions can initiate a T cell-mediated immune response. Thus, one of ordinary skill in the art can readily extrapolate the antibodies and methods described in the instant application to the claimed inventions with routine experimentation.

The Claimed Inventions and Alternative Embodiments

The Examiner maintains that the method steps are not differentiated and rejects appellants' argument that the use of an antibody as opposed to antibody-antigen conjugate differentiates the claimed method from disclosed alternatives. The Examiner further points to the additional evidence provided by appellants as "activating T-cells or inducing an immune response, not reducing an immune [response] as the claims recite."

First, as discussed above, the additional evidence submitted by appellants, e.g., *Pereira* et al., shows induced immune response in a completely different context from the claimed invention. As discussed above (as well as disclosed in the instant application as another, separate embodiment), an anti-DC-SIGN antibody can target DC *in vivo*, which appears to facilitate the targeting of antigens to DC for internalization and processing, allowing for more effective antigen presentation and induction of an immune response at a much lower concentration of the antigen. *See Tacken* et al. discussed above. This does not contradict the fact that DC and T cell interactions initiate the T cell-mediated immune response and that inhibiting the interaction can reduce the T cell-mediated immune response.

These two different methods as disclosed in the instant application – one for reducing an immune response and the other one for increasing an immune response – have clearly differentiating features. Only the first one is claimed here (the second is the subject matter embodied in the claims of U.S. Patent No. 7,285,642), and it should be noted first that these two different methods have distinct underlying mechanisms. The claims of the instant application are directed to reducing a T cell-mediated immune response and requires the use of an antibody that binds DC-SIGN on a dendritic cell to inhibit the interaction between the dendritic cell and a T cell. Accordingly, at least two mechanisms underlie the claimed method: i) the interaction between a dendritic cell and a T cell triggers the T cell-mediated immune response, and ii) DC-SIGN mediates the interaction between the dendritic cell and the T cell, which interaction is inhibited by an anti-DC-SIGN antibody. While the former has been textbook knowledge in the art, the instant application discloses the latter in detail, i.e., the instant

application teaches that DC-SIGN is a receptor on DC and is responsible for an interaction with ICAM-3 on T cells. It further teaches that blocking that interaction, e.g., by an anti-DC-SIGN antibody, prevents the activation of T cells.

The alternative embodiment taught in (but not claimed by) the instant application is directed to enhancing an immune response. The mechanisms underlying the alternative methods are also at least two fold: i) DC are professional antigen-presenting cells; and ii) antigens are processed by DC and then presented to neighboring T cells to generate an antigen-specific immune response. Thus, using an antibody that targets DC specifically helps "deliver" an antigen (e.g., an antigen conjugated with the antibody) to DC for better processing, resulting in an enhanced immune response to specifically targeted antigens.

Accordingly, the claimed method includes at least one clearly differentiating feature, that feature being that the anti-DC-SIGN antibody inhibits the interaction between a T cell and a dendritic cell, thereby reducing the T cell-mediated immune response, whereas the alternative embodiment involves the use of an anti-DC-SIGN antibody to target an antigen (in the form of an anti-DC-SIGN antibody-antigen conjugate) to DC for better antigen-presentation and enhanced antigen-specific immune response. Indeed, the latter anti-DC-SIGN antibody-antigen conjugate should preferably not lead to a reduced T cell-mediated immune response. It must be noted that the claims of the instant application do not recite an antibody-antigen conjugate or an enhanced antigen-specific immune response.

With respect to the Examiner's argument that the claims do not give guidance in defining the population to which the claims apply, appellants reiterate that this appears to be a new ground of rejection absent from the final rejections in the Final Office Action dated October 6, 2009 and Advisory Action dated January 5, 2010.[3] Whether such a new ground is appropriate or not, appellants maintain that one of ordinary skill in the art clearly understands the population of those in need of a reduced immune response. Additionally, claims 24 to 26 further specify certain populations in such a need.

Accordingly, the disclosure is commensurate with the claimed inventions: in view of the knowledge in the art, it provides specific and sufficient guidance for one of ordinary skill

[3] Again, appellants note that this rejection was raised in the non-final Office Action dated March 6, 2009.

in the art to extrapolate the teachings and knowledge to the claimed invention without undue experimentation.

V. Conclusion

For at least the foregoing reasons and the reasons set forth in appellants' Appeal Brief, appellants respectfully submit that claims 1, 3, 4, 6, 7, 19 and 23-27 are in condition for allowance. The Examiner's rejection of these claims should, therefore, be reversed.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 18-1945, from which the undersigned is authorized to draw.

Dated: October 5, 2010

Respectfully submitted,

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